The Renin-angiotensin System in Obesity and Vascular Diseases

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No relevant financial relationships exist.
Harriett Dustan

- Pioneer in clinical cardiovascular research
- 1st person to give sodium nitroprusside to humans,
- Thiazide diuretics potentiate blood pressure lowering of other antihypertensives,
- Definition of hemodynamics of primary aldosteronism,
- Pathophysiology of obesity-related hypertension

In Memoriam, Circulation 100:2122-2123, 1999
Acknowledgments: Lab/Trainees
The Ever Evolving RAS

Angiotensinogen

- Prorenin ↘️ Renin
  - (Pro)Renin Receptor
    - Signals
    - Activates Renin

- ACE
  - Angiotensin I (1-10) ↘️ Angiotensin II (1-8)
    - ACE
    - Angiotensin III (2-8)
      - Aminopeptidase A
      - Aminopeptidase N
        - Angiotensin IV (3-8)

ACE2
- Angiotensin I (1-10) ↘️ Angiotensin I (1-9)
- Angiotensin I (1-9) ↘️ Angiotensin I (1-7)

ACE
- Angiotensin I (1-10) ↘️ Angiotensin I (1-9)
- Angiotensin I (1-9) ↘️ Angiotensin I (1-7)

ACE2
- Angiotensin I (1-10) ↘️ Angiotensin I (1-9)
- Angiotensin I (1-9) ↘️ Angiotensin I (1-7)
Research Program

Angiotensin II

Adipose Tissue

Atherosclerosis

Hypertension

AAA

Reduced supply of blood

Exhaustion, weakness, pain

Vascular wall

Constriction
Expression of RAS components during adipocyte differentiation

Cocktail

Angiotensinogen

AT1 receptor

ACE2

Gupte et al., AJP 295: R781-8, 2008
## Prevalence

**Obesity* Trends Among U.S. Adults**

(*BMI ≥30)

<table>
<thead>
<tr>
<th>States with the Highest Obesity Rates</th>
<th>States with the Highest Rates of Adult Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rank</td>
<td>State</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
</tr>
<tr>
<td>1</td>
<td>Mississippi</td>
</tr>
<tr>
<td>2</td>
<td>West Virginia</td>
</tr>
<tr>
<td>3</td>
<td>Alabama</td>
</tr>
<tr>
<td>4</td>
<td>Louisiana</td>
</tr>
<tr>
<td>5</td>
<td>South Carolina</td>
</tr>
<tr>
<td>6</td>
<td>Tennessee</td>
</tr>
<tr>
<td>7</td>
<td>Kentucky</td>
</tr>
<tr>
<td>8 (tie)</td>
<td>Oklahoma</td>
</tr>
<tr>
<td>8 (tie)</td>
<td>Arkansas</td>
</tr>
<tr>
<td>10</td>
<td>Michigan</td>
</tr>
</tbody>
</table>

Source: CDC, Behavioral Risk Factor Surveillance System, February 2010
OBESITY

↑ Angiotensinogen (AGT)

↑ Angiotensin II

Hypertension

Frederique Yiannikouris, PhD
$Agt^{fl/fl}$, wild type, $Agt^{Ap2}$ adipocyte AGT deficient

AGT mRNA abundance

AGT protein

$Agt^{fl/fl}$, wild type, $Agt^{Ap2}$ adipocyte AGT deficient

AGT (ng/ml)
Adipocyte AGT deficiency has no effect on body weight, fat mass, or glucose tolerance.

\[ \text{Agt}^{fl/fl} = \text{controls} \]
\[ \text{Agt}^{ap2} = \text{Adipocyte AGT deficient} \]
Adipocyte deficiency of AGT ablates obesity-hypertension

Hypertension, in press, 2012
Reductions in plasma AngII in obese adipocyte AGT-deficient mice are paralleled by reduced adipose AngII content.
Summary

- Deficiency of AGT in adipocytes prevents obesity-induced increases in plasma AngII and obesity-related hypertension
- Tissue production of AngII (e.g., adipose) can be a significant source of circulating AngII in the setting of obesity and in the development of obesity-induced hypertension

*Hypertension*, in press, 2012
Why do adipocytes have AT1aR?

What does AngII do to an adipocyte?

Is this influenced by obesity and does it contribute to obesity-associated diseases?

Kelly Putnam

*Endocrinology, epub ahead of press, 2012*
Adipocyte deletion of the AT1aR

Floxed AT1aR Gene

AT1aR<sup>fl/fl</sup>

LoxP1 LoxP2 LoxP3

Exon 3 Neocassette

FLPE

AT1aR<sup>aP2</sup>

At1aR<sup>fl/fl</sup> At1aR<sup>aP2</sup>

AT1aR:18s

Liver Kidney Heart Brain Spleen BAT WAT

0.0 0.1 0.2

* * *

AT1aR gene deletion

Floxed AT1aR Gene

AT1aR<sup>fl/fl</sup>

LoxP1 LoxP2 LoxP3

Exon 3 Neocassette

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At1aR<sup>fl/fl</sup> At1aR<sup>aP2</sup>

AT1aR:18s

Liver Kidney Heart Brain Spleen BAT WAT

0.0 0.1 0.2

* * *

AT1aR gene deletion
Adipocyte AT1aR deficiency has no effect on the development of obesity, but...
Summary

• Adipocytes have AT1aR, but they play no major role in the development of obesity
• In lean mice, deficiency of AT1aR on adipocytes decreases adipocyte differentiation, resulting in hypertrophy of remaining adipocytes
OBESITY

AngII → ACE2 → Ang-(1-7)

Sean Thatcher, PhD
Assistant Professor

Manisha Gupte, PhD
Hypertension prevalence is greater in men than women before menopause: Are females protected against obesity hypertension?

<table>
<thead>
<tr>
<th>Age</th>
<th>Men (%)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-34</td>
<td>9.2</td>
<td>2.2</td>
</tr>
<tr>
<td>35-44</td>
<td>21.1</td>
<td>12.6</td>
</tr>
<tr>
<td>45-54</td>
<td>36.2</td>
<td>36.2</td>
</tr>
<tr>
<td>55-64</td>
<td>50.2</td>
<td>54.4</td>
</tr>
<tr>
<td>65-74</td>
<td>64.1</td>
<td>70.8</td>
</tr>
<tr>
<td>75 and older</td>
<td>65.0</td>
<td>80.2</td>
</tr>
<tr>
<td>All</td>
<td>31.8</td>
<td>30.3</td>
</tr>
</tbody>
</table>

CDC Menopause
Female mice gain more weight and fat mass than males but are protected from obesity-hypertension.

Arteriosclerosis, Thrombosis and Vascular Biology 32:1392-9, 2012

*, P<0.05 compared to LF
**, P<0.05 compared to male
The AngII/Ang-(1-7) balance is different between obese males and females, and ACE2 deficiency promotes hypertension in both sexes.
Summary

• ACE2 is important in regulating the AngII/Ang-(1-7) balance in the development of obesity-hypertension

• Females rule!, they are protected against obesity-hypertension potentially through an ACE2-dependent mechanism
AAA

• 13\textsuperscript{th} leading cause of death in the United States

• Risk factors
  – Male Gender
  – Smoking
  – Age >65
  – Family history
  – Hypertension
  – Obesity

• No pharmacologic treatments for AAA
  • Surgical repair is the only therapeutic option to prevent rupture (> ~ 5.0 cm)

AngII-induced Vascular Pathology

Angiotensin II

Osmotic mini-pump

28 days

apoE-/-

LDLr-/-

AAA

Atherosclerosis

Risk Factors: Effects of Male Gender

Hypothesis:
Sex hormones mediate gender differences in AngII-induced vascular diseases by regulating the AT1a receptor

Xuan Zhang, PhD
Androgen is the primary regulator of AAA susceptibility in male mice through regulation of aortic AT1αR

Testosterone is the mediator
Aortic Development

Adapted from Majesky M. ATVB 2007
Can we turn a female into a male with enhanced AAA susceptibility by exposing her to testosterone early in life?

Day 1

Testosterone (400 µg/mouse) or Vehicle

10-12 weeks

• Aortic gene expression
• AngII infusion

Neonatal testosterone strikingly promotes AngII-induced AAAs in adult female mice.
Summary

• Testosterone has pronounced effects during development to influence the vasculature.

• AT1a receptors are a target of testosterone in smooth muscle cells to influence vascular remodeling in aneurysm formation.

• Vascular disease is sexually dimorphic.
Acknowledgments: Grant Support

- NIH HL73085 (LAC)
- NIH HL107326 (LAC)
- NIH P01 HL080100 (AD, LAC)
- NIH P42 ES007380 (BH, LAC)
- NIH T32 DK007778 (LAC)
- NIH P20 GM103527 (LAC)
- AHA: 0815419D (MG), 11PRE6760002 (KP), Pre0815513D (XZ), 12PRE12050430 (RS)